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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,762	12/27/2005	Massimo Ferrari	207,385	8763

7590 08/15/2011
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EXAMINER

MABRY, JOHN

ART UNIT	PAPER NUMBER
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1625

MAIL DATE	DELIVERY MODE
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08/15/2011

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/562,762	Applicant(s) FERRARI ET AL.
	Examiner JOHN MABRY	Art Unit 1625

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 February 2011.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 26-43 and 47-49 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 26-43 and 47-49 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____. | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) <input type="checkbox"/> Notice of Informal Patent Application
6) <input type="checkbox"/> Other: _____. |
|--|--|

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 23, 2011 has been entered.

Response to Applicant's Remarks

Applicant's response on February 23, 2011 filed in response to the Final Office Action dated September 3, 2011 has been received and duly noted.

In view of this response, the status of the rejections/objections of record is as follows:

Status of the Claims

Claims 26-43 and 47-49 are pending and rejected.

Claims 1-25 and 44-46 have been cancelled.

Withdrawn Rejection

Claim Rejections - 35 USC § 103

Claims 26-46 and 47-49 rejections are withdrawn under 35 U.S.C. 103(a) as being unpatentable under 35 U.S.C. 103(a) as being unpatentable over Alt (US 5,512,684) in view of Gandolfi et al (US 4,999,362) and in view of Dorwald (Side Reactions in Organic Synthesis 2005, Wiley-VCH, page 2).

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

A new rejection under 35 U.S.C. 103(a) as being unpatentable under 35 U.S.C. 103(a) as being unpatentable over Alt (US 5,512,684) in view of US 5,629,425 (LaBell) and in view of Dorwald (Side Reactions in Organic Synthesis 2005, Wiley-VCH, page 2) is shown below:

The instant application claims a process for the preparation of raloxifene hydrochloride (I) by reaction of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (II) to make 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene (III) then protecting with an acetylating agent, particularly acetic anhydride in presence of triethyl amine, to produce the corresponding 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV). The 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) is acylated with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride with aluminum chloride in halogenated solvent, in particularly methylene chloride, to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene (VI) without isolating the product. The 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene is deprotected by hydrolysis with treatment of alkaline hydroxide in alcohol solvent, in

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particular sodium hydroxide followed by treatment of strong acid, particularly hydrochloric acid to obtain the corresponding 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride, I).

Scope & Content of Prior Art MPEP 2141.01

Alt describes a process as illustrated in Scheme III (columns 5/6) for the preparation of raloxifene hydrochloride (I) by reaction of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene (II) (R=C1-C6 alkyl, column 2, lines 8-9 and see “Dealkylation” in column 7) to make 6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thiophene (III) then protecting with an acetylating agent, particularly acetic anhydride in presence of triethyl amine, to produce the corresponding 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) (see “Reprotection” in bottom of column 7 column 8, lines 1-5). The 6-acetoxy-2-(4-acetoxyphenyl)benzo[b]thiophene (IV) is acylated with 4-(2-piperidinoethoxy)benzoylchloride hydrochloride with aluminum chloride in halogenated solvent, in particularly methylene chloride, to obtain 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene (VI) then isolating the crude product (see “Acylation” in column 9, lines 22-23, lines 37-41). The 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene (VI) is deprotected by hydrolysis with treatment of alkaline hydroxide in alcohol solvent, in particular sodium hydroxide followed by treatment of strong acid, particularly hydrochloric acid to obtain the corresponding 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene – the desired product (see “Deprotection of

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Reprotected Dihydroxythiophenes” in bottom of column 10 - column 11, lines 63-67 and lines 1-22).

Experimentally, the deprotection of 6-acetoxy compound is converted to the deprotected 6-hydroxy compound by addition of sodium hydroxide in methanol. The solvent was then removed, extracted with organic solvent, acidified to pH 2-3 then made basic and continually worked up to yield a solid under vacuum. The crude product was purified by crystallization and column chromatography to yield the desired product in pure form (see column 15, lines 29-67 and column 16, lines 1-48).

US '425 describes both a “step-wise” (see Scheme V in columns 8 and 9) and preferably a “one-pot” synthesis (see Scheme V in columns 9 and 10) of the desired raloxifene HCl of Formula I using very similar intermediates and process as claimed.

US '425 describes the crystallization of the desired product of Formula I (raloxifene HCl). In the one-pot process, the 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene is deprotected by hydrolysis with treatment of alkaline hydroxide in alcohol solvent, in particular sodium hydroxide followed by treatment of strong acid, particularly hydrochloric acid to obtain the corresponding 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride, I) (see Scheme V in columns 9 and 10 and Examples 1-12 in columns 17-24).

Differences between Prior Art & the Claims MPEP 2141.02

Alt differs from the instant application in the following ways.

(a) Alt isolates the crude product, 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) prior to converting to desired product (I) versus Applicant's did not isolate 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI).

(b) The instant application describes a crystallization of the final product compared to Alt's acid-base work up and chromatography purification and

Prima Facie Obviousness, Rational & Motivation MPEP 2142-2413

It would be obvious to one of ordinary skill in the art at the time when the invention was made to initiate the synthesis of the desired final product, 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene hydrochloride (raloxifene hydrochloride) by the process as described by Alt.

(a) Alt differs from the instant application in the following ways. Alt isolates the crude product, 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI) prior to converting to desired product (I) versus Applicant's did not isolate 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]-benzo[b]thiophene (VI).

US '425 describes both a "step-wise" (see Scheme V in columns 8 and 9) and preferably a "one-pot" synthesis (see Scheme V in columns 9 and 10) of the desired raloxifene HCl of Formula I using very similar intermediates and process as claimed.

Additionally, it is well within the purview of the skilled artisan in the relevant art to reduce steps in order to achieve the desired product faster and in higher yields.

Dorwald clearly states that in the design of an organic molecule, a synthetic chemist would need to analyze *“the shortest synthetic strategies which are most likely to give rapid access to the target compound, ideally in high yield and purity”* – see page 2 under 1.2 Synthesis Design.

Again, an artisan of ordinary skill, in this case, an organic chemist, would be motivated to take the prior art of Alt '684 in view of US '425 and reduce the step of isolation of 6-acetoxy-2-(4-acetoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene (VI) in order to achieve the final product (I) in greater yield and higher purity.

Furthermore, Alt suggests that HCl salt formation of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzo[b]thiophene is conveniently formed by reacting the compound with hydrochloric acid which are quickly formed in high yields. These salts are formed by isolating the compound from a suitable acid wash as the final step of the synthesis. The preferred salt is the hydrochloric salt (see column 12, lines 35-67 and column 13, lines 1-6).

The procedure, steps of synthesis and reactions conditions are all described that would motivate one of ordinary skill in the art to make minor and obvious experimental adjustments in order to achieve high yields and high purity of desire product, (I).

Claims 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over GB 2293382 in view of Hartauer et al (Pharmaceutical Development and Technology 2000, 5 (3), 303-310).

Scope & Content of Prior Art MPEP 2141.01

GB '382 discloses raloxifene hydrochloride with a purity of 99.4% (see Example 8 on page 30).

GB '382 also discloses raloxifene hydrochloride free of aluminum contaminants (see page 1, lines 27-30).

Hartauer et al discloses that raloxifene N-oxide is a known impurity (degradation product) of raloxifene hydrochloride (see Figure 1 on page 306, Figure 4 on page 309 and entire reference).

Differences between Prior Art & the Claims MPEP 2141.02

GB '382 differs from the instant application in the percentage of purity:

- (a) GB '382's 99.4% versus Applicant's 99.7% - a 0.3% difference (claim 41).
- (b) GB '382's raloxifene N-oxide less than 0.01% versus Applicant's 99.7% - a 0.3% difference (claims 42 and 43).

Prima Facie Obviousness, Rational & Motivation MPEP 2142-2413

The instant application crystallizes the crude raloxifene HCl from water and methanol two times (see Examples 3 and 4 on pages 9 and 10 of the Specification).

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GB '382 discloses crude raloxifene HCl crystallized from water and methanol one time (see Example 8 on page 30, lines 19-31). An artisan of ordinary skill would be motivated to crystallize the raloxifene HCl multiple times (using the same crystallization solvent system) in order to achieve an increased level of purity.

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that “[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include:

- (A) Combining prior art elements according to known methods to yield predictable results;
- (B) Simple substitution of one known element for another to obtain predictable results;
- (C) Use of known technique to improve similar devices (methods, or products) in the same way;
- (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

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- (E) “Obvious to try” – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
- (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
- (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. See MPEP § 2143 for a discussion of the rationales listed above along with examples illustrating how the cited rationales may be used to support a finding of obviousness. See also MPEP § 2144- §2144.09 for additional guidance regarding support for obviousness determinations.

The aforementioned reasons above describe rationales that support a conclusion of obviousness based upon the KSR International Co. v. Teleflex Inc. decision.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should

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you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's primary examiner can be reached at (571) 272-0684, first, or the Examiner's supervisor, Janet Andres, PhD, can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Rita J. Desai/

Primary Examiner, Art Unit 1625

/John Mabry/
Examiner
Art Unit 1625